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The application was originally filed in English.

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(21) *Patentansökningsnummer* / *Patent application number* — *9702066-3*

(86) *Ingivningsdatum* / *Date of filing* — *1997-05-30*

Stockholm, 1998-06-10

För Patent- och registreringsverket
For the Patent- and Registration Office

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Avgift
Fee

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A NEW SALT

Field of the Invention

The present invention relates to a new salt of a compound, namely (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, in particular the monohydrate of this salt. The invention also relates to processes for the manufacturing of said salt, the use of said salt in the manufacture of pharmaceutical formulations, and to the use of said salt in medicine, especially in the form of the monohydrate.

Background of the Invention

The compound (*R*)-5-carbamoyl-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran, which also may be named (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide and pharmaceutically acceptable salts thereof are described in WO 95/11891.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable salts of the compound. Example of such acids are hydrochloric acid, hydrobromic acid as well as lactic acid and tartaric acid etc.

The disclosed hydrochloride salt of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide is too hygroscopic and thus physically instable during manufacturing as well as during storage to be an appropriate salt for the drug.

Disclosure of the Invention

It has now surprisingly been found that the salt (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate in the form of the anhydrate, hemihydrate or monohydrate is physically more stable during storage than the hydrochloride salt of said compound, since the tartrate forms of the said compound are not disposed to absorb water to the same degree as the hydrochloride salt of the same compound, i.e. the tartrates are less hygroscopic. The salt, (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate anhydrate, is not physically stable enough because during storage under normal humidity conditions, it can absorb water from the surrounding atmosphere resulting in an undefined hemihydrate. This property of absorbing water is also a problem during manufacturing of e.g. solid pharmaceutical dosage forms such as tablets and hard gelatine capsules. In these processes granulation with e.g. aqueous polymer solutions is common, and absorption of water to the tartrate salt results in an undefined hemihydrate.

In spite of the generally good solubility and dissolution properties of the tartrate salt from e.g. oral drug delivery point of view, the anhydrate form is not suitable from a quality assurance point of view due to its hygroscopicity under normal humidity conditions.

The monohydrate of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate has surprisingly been shown to be physically stable under normal humidity conditions, i.e it is not hygroscopic. Consequently, the monohydrate is suitable for long term storage and is easier to work with in the production of different solid pharmaceutical dosage forms.

The good solubility and dissolution properties of the anhydrous tartrate salt are even more pronounced for the monohydrate of the *(2R,3R)*-tartrate salt. The water is firmly bound in the crystal lattice and is not released even upon heating up to 70 °C. This is well above the commonly used process temperatures e.g. during the granulation process in the production of tablets and hard gelatine capsules.

Accordingly, the present invention relates to the crystalline salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, and more specifically to the stable crystalline salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate.

The salts of the invention may be used as a selective 5-HT_{1A} receptor antagonists in in the treatment of CNS disorders and related undesirable medical conditions. Examples of such disorders are depression, anxiety, obsessive-compulsive disorder (OCD), anorexia, bulimia, senile dementia, migraine, stroke, Alzheimer's disease, cognitive disorders, hypertension, thermoregulatory and sexual disturbances, pain, disturbances in the cardiovascular system and gastrointestinal disorders.

The novel crystalline salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, and especially the monohydrate of said tartrate salt may also be formulated into various dosage forms for oral, parenteral, rectal and other modes of administrations.

Examples of formulations are tablets, pellets, granules, capsules (e.g. hard gelatine capsule), aqueous solutions and suspensions.

Usually the active ingredient will constitute between 0.0001 to 99% by weight of the formulation, more specifically between 0.001 and 30% by weight of the formulation.

To produce pharmaceutical formulations containing the active ingredient of the invention in the form of dosage units for oral applications, the active ingredient may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or poly-vinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, sodium

tablets. The active ingredient may be granulated together with excipients using an aqueous or organic solution of binders, dried and screened prior to tablet compression.

If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelantine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to a person skilled in the art,that is dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different amounts of active ingredient.

For the preparation of hard gelatine capsules, the active ingredient may be processed in the form of granules, and may be admixed with the excipients mentioned above for tablets.

For the preparation of soft gelatine capsules, the active ingredient may be admixed with e.g. a vegetable oil or polyethylene glycol.

Suppositories for rectal administration may be prepared by dissolving or suspending the active ingredient in a molten suppository base such as Witepsol® followed by casting and cooling.

Gelatine rectal capsules, may comprise the active ingredient in admixture with vegetable oil or paraffin oil and may contain the polymers and/or dyestuff mentioned above.

Aqueous solutions for parenteral or oral administration are produced by dissolving the active compound of the invention in water, adjusting pH and ionic strength with common buffering agents such as citric acid, phosphoric acid or other similar acids and commonly used salts of them, sodium carbonate, hydrogen carbonate or other similar salts or hydrochloric acid or sodium hydroxide. In the case of parenteral solutions the sterility is ensured by final heat sterilization or e.g. sterile filtration. Lyophilization may also be used resulting in a reconstitutable solid product.

Suitable daily doses of the salt of the invention in therapeutical treatment of humans are about 0.001-100 mg/kg body weight.

The specific processes for manufacturing (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, more specifically the monohydrate thereof, is a further aspect of the invention.

The process for manufacturing the new salt form (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, more specifically the monohydrate thereof, can be described in the following way:

i) dissolving (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide in an approriate organic solvent, optionally by heating,

ii) adding *(2R,3R)*-tartaric acid dissolved in an appropriate aqueous or non-aqueous solvent,

iii) allowing the obtained solution to stand cold to crystallize,

iv) recrystallizing in an aqueous organic solvent, if a non-aqueous solvent is used in step ii), to obtain the tartrate monohydrate salt.

A more detailed illustration of the process of manufacturing is presented in Examples 1 and 2.

Starting from the anhydrate or a mixture of anhydrate and hemihydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, obtained by any suitable process, then recrystallize said tartrate in an

Appropriate solvents to dissolve (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide may be organic solvents such as tetrahydrofuran, diethyl ether, acetone, ethanol, methanol and other alcohols.

Appropriate aqueous organic solvents used in the crystallization or recrystallization may be alcohols, nitriles, esters, or ketone e. g. methanol, ethanol, isopropanol, acetonitrile, or acetone, preferably acetone.

Example 1

(*R*)-3-*N,N*-Dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide Hydrogen (2*R*,3*R*)-Tartrate

(*R*)-3-*N,N*-Dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide (100 mg, 0 31 mmol) was dissolved in tetrahydrofuran (1 mL) by heating and the solution was diluted with diethyl ether (25 mL). To this solution was a *(2R,3R)*-tartaric acid (55 mg, 0.35 mmol) solution (made by dissolving *(2R,3R*)-tartaric acid in tetrahydrofuran (1 mL) and diluting with diethyl ether (25 mL)) added, the milky solution was filtered and allowed to stand in the refrigerator overnight. The solid was filtered and dried in a vacuum oven to give 142 mg white crystals (98% yield) Mp 174-180°C (DSC). Anal. Calcd. for $C_{22}H_{23}FN_2O_8$: C, 56.4; H, 6.2; N, 6.0. Found: C, 56.2; H, 5.9; N, 5.6.

Example 2.

(*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide Hydrogen (2*R*,3*R*)-Tartrate Monohydrate

(*R*)-3-*N,N*-Dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide (2.0 g, 6.3 mmol) was dissolved in tetrahydrofuran (5 mL) by heating and the solution was

diluted with diethyl ether (400 mL). To this solution was a *(2R, 3R)*-tartaric acid (1.1 g, 6.9 mmol) solution made by dissolving *(2R, 3R)*-tartaric acid in tetrahydrofuran (15 mL) and diluting with diethyl ether (300 mL)) added and the clear solution was allowed to stand in the refrigerator over the weekend. The crystalline solid was filtered and recrystallized from 1.5% aqueous acetone (400 mL) to give 2.6 g sparkly crystals (85% yield). Mp. 174-180°C (DSC). Anal. Calcd. for $C_{22}H_{25}FN_2O_9$: C, 54.3; H, 6.4; N, 5.8. Found: C, 54.4; H, 6.3; N, 5.6.

The melting point (Mp) was measured by using differential scanning calorimetry (DSC).

Thermogravimetric measurements performed shows that the anhydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate has an initial weight loss of 0.997% w/w. The initial weight loss of 4.104% w/w for the monohydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate compares favourably with the theoretical water content of a monohydrate.

X-Ray Diffraction

X-ray intensity data were collected on a single-crystal *MACH3/CAD4* diffractometer (Enraf-Nonius, 1994) equipped with graphite monochromatic CuK(α) radiation and a proportional scintillation counter. The structure was solved by direct methods, *SIR92* (Altomare, Cascarano, Giacovazzo & Guagliardi, 1992) and refined with full-matrix least-square methods, *LSFM* (Hansen & Coppens, 1974) within the *MolEN* software package (Straver & Schierbeck, 1994). All non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms not involved in short intermolecular contacts were fixed from a late difference Fourier and supplied with isotropic displacement parameters, U_{iso} = 0.06 Å^2. Hydrogen atom positions involved in H-bonding were refined freely and assisted with a

fixed isotropic temperature factors, U_{iso} = 0.06 Å^2, except for the crystal water hydrogens, U_{iso} = 0.07 Å^2.

Figure 1 shows the three-dimensional structure and absolute configuration of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide in relationship to the (2*R*,3*R*)-tartrate portion and the water molecule.

Stability

The stability of the monohydrate of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate compared to the anhydrate of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate as well as compared to the HCl-salt regarding moisture absorbtion has been set as a measure of physical stability of the product.

The moisture sorption analysis, absorption and desorption, was performed using a VTI microbalance, Model MB300W (VTI Corporation, USA) linked to an IBM PC. The relative humidity (RH) within the balance was monitored using a dew point analyser. Approximately 10 mg of substance was dried to constant weight at 60°C and then exposed stepwise to RH of between 5 to 90% at 25°C, the step interval being 5%. The desorption profile was also obtained.

Figure 2 shows the moisture sorption curve of the HCl salt of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide. As seen from the figure the HCl salt takes up a considerable amount of moisture at high relative humidities. At 85% relative humidity the HCl salt has taken up approximately 20% w/w and exhibits deliquescence.

Figure 2 also shows the moisture sorption curve of the anhydrate (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen

(2*R*,3*R*)-tartrate. As seen from the figure, the anhydrate absorbs moisture readily. At a RH of 90% about 4.2 % (w/w) moisture was absorbed. The desorption profile (the upper part of the curve) indicates that the moisture taken up is firmly bound and that the sample has formed a monohydrate.

Figure 2 shows the moisture sorption curve of the monohydrate of (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate. As seen from the figure the monohydrate absorbs only 2.5% (w/w) at 90% RH. Significant uptake of moisture was only recorded at RH of approximatelt 60% or above. The desorption profile shows that the moisture uptake is reversible.

CLAIMS

1. The salt (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate.

2. The salt (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate.

3. A pharmaceutical formulation containing, as active ingredient, the salt according to claims 1 or 2 in association with a suitable diluent, excipient or an inert carrier.

4. A pharmaceutical formulation according to claim 3 for oral administration.

5. The salt according to claims 1 or 2 for use in therapy.

6. The use of the salt according to claims 1 or 2 in the manufacture of a medicament in the prevention or in the treatment of CNS disorders and undesirable medical conditions.

7. The use according to claim 6 in the manufacture of a medicament in prevention or in the treatment of 5-HT_{1A} receptor antagonist activity realted CNS disorders and undesirable medical conditions.

8. The use according to claim 7 in the manufacture of a medicament in the prevention or in the treatment of depression.

9. The use according to claim 7 in the manufacture of a medicament in the prevention or in the treatment of anxiety.

10. A method for prevention or the treatment of CNS disorders and undesired medical conditions comprising administration, to a host in need of such treatment, an effective amount of the salt according to claims 1 or 2.

11. A method according to claim 10 for prevention or the treatment of 5-HT_{1A} receptor antagonist activity related CNS disorders.

12. A method according tp claim 11 for the prevention or the treatment of depression.

13. A method according to claim 11 for the prevention or the treatment of anxiety.

14. A process for the manufacture of the salt as defined in claims 1 or 2 characterized by the following consecutive steps:

i) dissolving (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate in an approriate solvent, optionally by heating,

ii) adding *(2R, 3R)*-tartaric acid dissolved in an appropriate aqueous or non-aqueous organic solvent,

iii) allowing the solution obtained to stand cold to crystallize,

iv) recrystallizing in an appropriate aqueous organic solvent, if a non-aqueous solvent is used in step ii), to obtain the salt defined in claim 2.

15. A process for the manufacture of the salt as defined in claim 2 characterized by recrystallizing *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3, 4-dihydro-*2H*-benzopyran-5-carboxamide hydrogen *(2R, 3R)*-tartrate in an appropriate aqueous organic solvent.

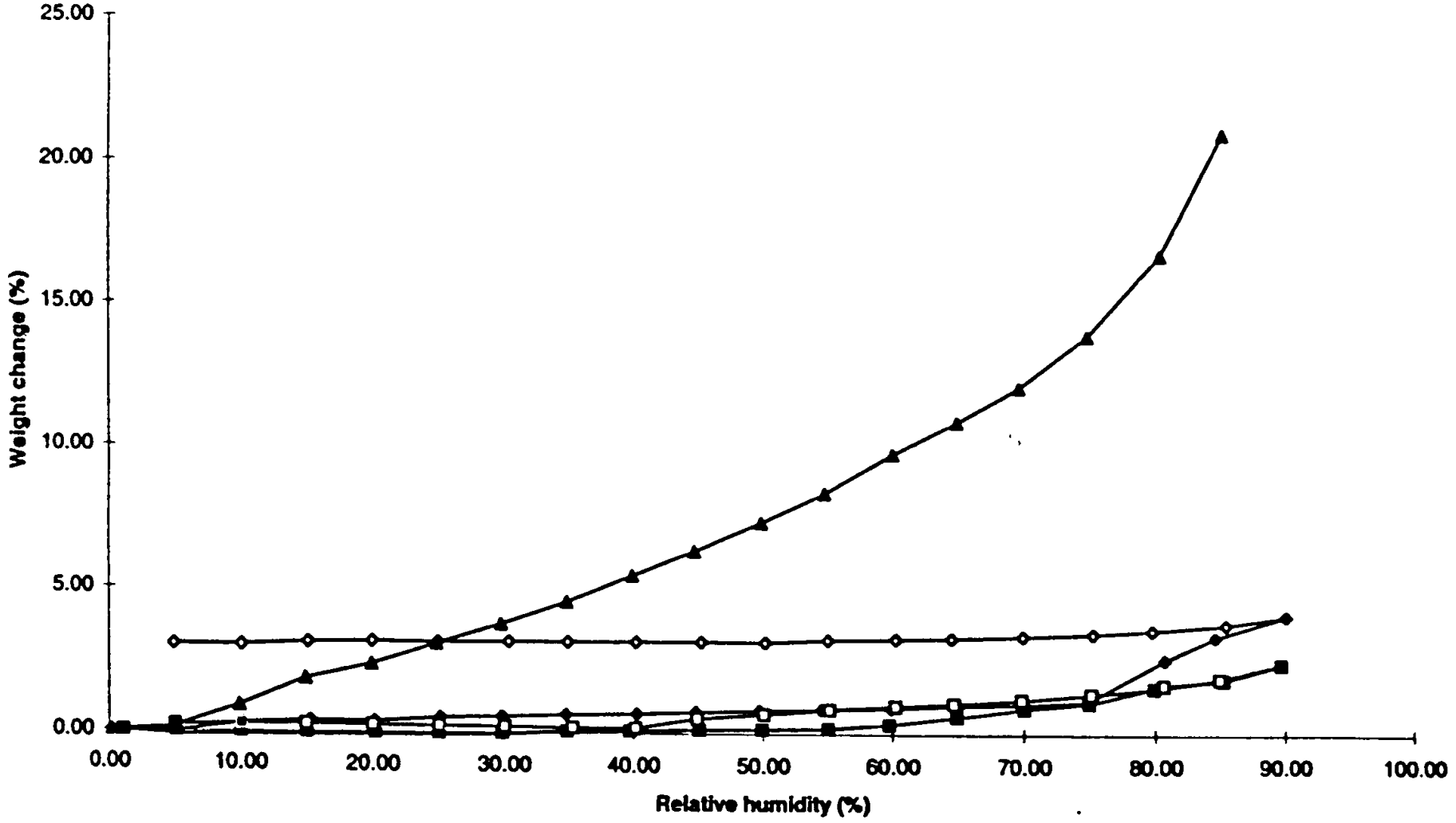
16. A process according to any one of the claims 14 or 15, wherein the aqueous organic solvent is aqueous acetone.

Abstract

A new salt (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, especially (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate, processes for the manufacturing of said tartrate salt, the use of said salt in medicine, the use of said tartrate salt in the manufacture of pharmaceutical formulations, and a method for the treatment of CNS disorders by administration of said tartrate salt to a host in need such treatment.

Figure 2. Moisture sorption profiles for —◆— Tartrate anhydrate —■— Tartrate monohydrate —▲— HCl

Open symbols show the desorption profiles



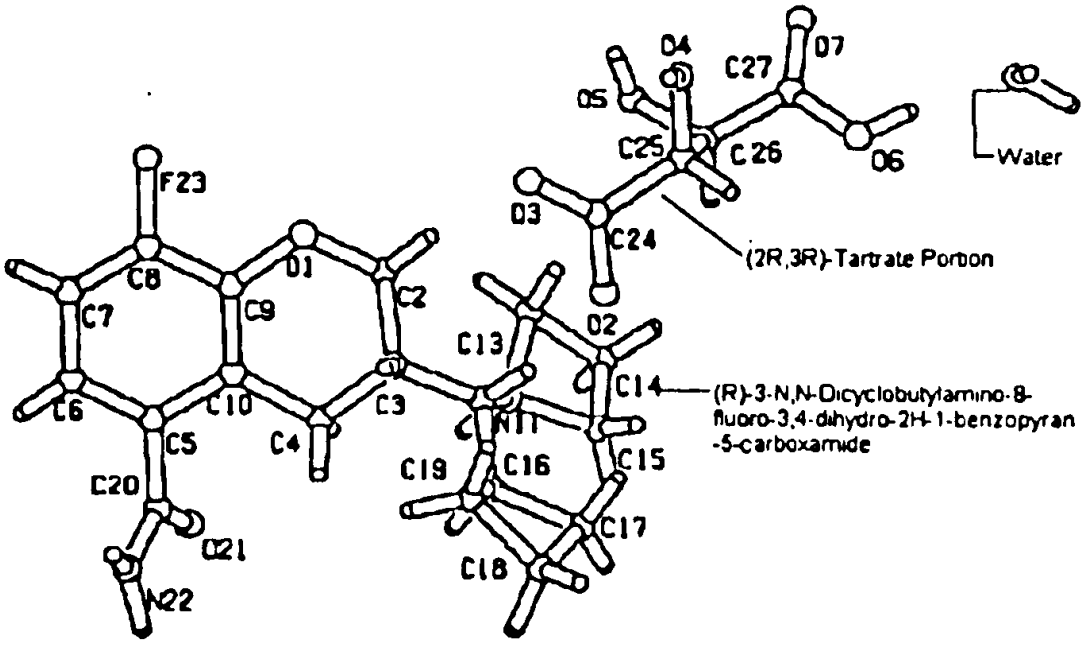


Figure 1